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ORIGINAL MEMOIRS.

ON THE MORPHOLOGY OF CARCINOMA AND THE PARASITIC THEORY OF ITS ETIOLOGY.¹

BY GEHEIM-MEDIZINALRATH PROFESSOR DOCTOR
JOHANNES ORTH,

OF BERLIN,

Professor of Pathology in the University of Berlin.

(Translated from the German of the author's manuscript by PAUL
MONROE PILCHER, M.D.)

IN complying with the urgent invitation with which I have been honored, I accept the subject of Carcinomatous New Growths as the theme of an address. I cannot offer anything that is new, but it may, however, be of certain interest to hear the views of a pathologist who believes himself to be essentially in accord with the majority of German pathologists concerning two fundamental questions, which are as follows:

I. In what way is cancer morphologically characterized?

II. What can be said concerning the parasitic origin of the disease?

I. With regard to all that the first question involves, there can be no doubt that the characteristic and distinguishing features of the cancer cells are that they are none other than epi-

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thelial cells. They are epithelial cells not only in accordance with their structure, with respect to the nature of their protoplasm and nuclei, not only epithelium in accordance with their biological activities, but they are also epithelium in accordance with their origin.

There is no metaplasia from connective-tissue cells or cells of that nature into epithelial cells, into cancer cells; it is true that one kind of epithelium can be transformed into another kind, for example, cylindrical cells into squamous cells, squamous cells into cylindrical cells, but an epithelial cell can never be made from a connective-tissue cell, and, *vice versa*, a connective-tissue cell can never be transformed into an epithelial cell.

However, in primary cancer it is difficult to prove the direct derivation of cancer cells from preformed epithelium, for the growth of a cancer is one thing, and its first inception is another. I am, I confess, of the opinion that there are cancers in which the transformation of preformed epithelial cells into cancer cells takes place continuously in the tissue bordering upon the margin of primary tumors, also that there are multicentric cancers, not only in the sense that the cancer change takes place at the same time in different neighboring spots, but also in such a manner that one spot becomes cancerous later than another. However, at the same time, I recognize that many cancers are unicentric, that they have arisen from a single-cell complex only, and possess only an interstitial but no contiguous growth. Formerly, a transformation of preformed epithelium into cancer was generally accepted without further investigation, as soon as a connection between such epithelium and cancer cells was present. That an assumption of this kind is not admissible, Ribbert has justly called attention to, since it is possible for cancerous epithelium to grow somewhere near preformed epithelium and become secondarily annexed to it. One dare not go so far, however, as to attempt to explain in this manner every connection between cancer cells and normal epithelium which one finds on the border or in the immediate neighborhood of a cancer; for by means of serial sections one

can often clearly demonstrate that an isolated deep growth of preformed cells appears, in which, while they closely resemble the mother cells, there is visible at the same time a certain difference. That thereby a particular kind of karyomitosis may be detected similar to the mitosis of the fertilized egg, concerning which I am not as yet entirely convinced, but undoubtedly in connection with this, changes in the condition of cells in regard to pigment do present themselves, as is most easily demonstrated in cancers of the gastro-intestinal tract. Not every appearance of growth in preformed epithelium can be regarded as the beginning of a cancerous change, for there is to be found on the border and in the neighborhood of cancer, just as of other rapidly growing tumors, a multiplication of cells as well as the formation of glycogen, which are only expressions of purely hyperplastic processes; but if a distinct plug-like ingrowth into the underlying tissue with a change of the cell body can be demonstrated, then one can consider it a primary cancerous change.

The origin of cancer cells from preformed epithelium can be recognized with most certainty in the very young cancers, and for this reason the work of Dr. Bormann, Ribbert's assistant, in collecting and carefully examining such cases, was most important. In his work which appeared recently he produces proof for the epithelial origin of the cancer cells in very young primary cancers.

A strong support for the conclusion that all cancer cells originate in regular succession (by inheritance) from preformed epithelium is supported by the secondary cancers of this kind, for they demonstrate, by the innumerable mitoses which the cancer cells show, how vigorously these multiply, so vigorously that the entire growth of these secondary growths can in this way be entirely explained. They demonstrate in the beginning, by the appearance of the first cancer cells in the lymph spaces of the lymphatic glands, by the presence of cancer cells in blood-vessels, that detached cancer cells represent the foundation, the starting-point of new cancerous nodules. It can always be shown by investigation of serial sections, especially

in embolic formation of cancers in the lung or in the liver, that a cancerous exuberant growth in the neighborhood of the vessels always takes its exit from a cancerous growth through the wall. There is no contact infection by way of the tissue surrounding the vessel through the intact wall of the vessel; but a continuous connection between the embolus and the perivascular cancer is always present; the embolus has by uninterrupted increase of its cells grown through the wall into the surrounding tissue.

Of very special importance for the assumption that all the cells of a secondary cancer have arisen from detached cells of an already existing cancer is the suppression of the local cells at the point of the new growth. As one can most easily demonstrate in the case of cancer of the liver, the local cells, the liver cells have nothing at all to do with the new growth of the cancer cells; they remain entirely passive, become displaced by the uninterrupted increase of the cancer cells, atrophy, and finally disappear.

All this goes to prove that the epithelial cancer cells form the essential element of the cancer; but they are not only the most important, but indeed the *ONLY* important, element. The tissue, other than this which is present in the cancer, the stroma, is without any significance for the organization of the cancer. There can be cancerous new growth without this stroma: in the so-called lymph-vessel cancers, that is to say, exuberant growths of cancer cells in the lumen of the lymph-vessels, which are seen in the lung, uterus, and other places, the lymph spaces, or greatly dilated lymph-vessels, for some distance are filled with cancer cells, without the presence of a trace of stroma. In other cancers the local tissue can take the place of stroma; in this manner cancerous growths are found in the lung in which the alveolar net-work immediately takes the place of the cancer stroma; in intravascular or infiltrating cancer of the liver the liver tissue itself, the liver cells with the interstitial connective tissue, forms the cancer stroma. In other cases the cancer stroma is also a new structure, as illustrated most clearly in many cancers of the ductus thoracicus in which the lumen

of the dilated duct contains not only cancer cells, but also a stroma, which is made up of entirely new-formed tissue, but tissue which has developed from the nearest local tissue, namely, from the wall of the vessel. Professor Williams, of Buffalo, investigated such a case at my institute in Goettingen, in which there were present in the stroma also elastic fibres, whose connection with the elastic tissue of the wall of the duct could be satisfactorily demonstrated.

The conclusion to be drawn from all this is that the stroma is an absolutely non-essential, accessory, and unimportant constituent of the cancer, even though in single instances the stroma may have a certain significance in determining the variety or character of the cancer. That, however, a scirrhus in its essentials (characteristics, organization) does not differ from a medullary, soft cancer is very clearly shown from the fact that the periphery or the metastasis of a scirrhus may be throughout of a softer medullary quality.

If, however, according to what has been said, epithelial cells originating in uninterrupted succession from preformed epithelium are the only essential thing in cancer, then from a scientific stand-point, and in accordance with the customary nomenclature, every cancer must be designated as *EPITHELIOMA*. In order to differentiate it from other epithelial new growths, it can be designated as malignant, destructive, or as *ABERRANT EPITHELIOMA*, the distinction being that in cancer epithelial cells are found in localities where epithelium does not normally exist. Where sharp boundary lines exist in an organ between the epithelial and non-epithelial portions, as in the stomach and intestines, it is easy to establish the aberrancy of the cancer cells; in other places it is especially the occurrence of portions of tissue enclosed within the masses of cancer cells, principally of elastic and collagen (collogenen) fibres, which prove that the cancer cells are present in a place where they do not belong, that as a disturbing element they have crowded into the tissue.

A further consequence of the epithelial nature of cancer is this, that the variety of the cancer must be determined by the

special characteristics of the epithelial cancer cells in the particular growth. It is of great significance, therefore, that in every deviation of the cancer cells from the normal epithelium, without exception, in the primary growths as well as in the metastases, there is found to be a definite character in the arrangement and in the morphological as well as the biological character of the cells.

In accordance with this, two groups of aberrant epithelioma may be distinguished:

1. Those with *typical arrangement of the cancer cells*.
2. Those with *atypical arrangement of the cells*.

To the first group belong (*a*) cancers, which follow the glandular type, *adenomata*, built up principally from cylinder cells, which form glandular ducts (canals) and complicated glandular structure, and which not infrequently produce a kind of secretion, especially in the stomach and intestines, a slimy secretion. (*b*) Cancers, whose cells, with respect to form, transformations, and arrangement in strata, are like the *epidermis*, and which for a long time have borne the name *cancroid*. It is of special importance for the theory that all cancer cells of the metastatic growth originate from cells of the primary growth, that just as in this first group of cancer, in the adenomata as well as in cancroids, the cells in the metastases show the same form and the same arrangement or transformation and stratification as those of the corresponding primary growth.

The second group is composed of cancers whose cells are placed together irregularly and in masses and patches (strings, cords, etc.), which therefore show an *atypical arrangement*, whose cells also show fewer distinct peculiarities, of which, however, it can well be said that they differ according to the particular organs in which the parent growth originated. I should like to designate this form of cancer by the word which has for its root the word *cancroid*, *i.e.*, *cancer*.

There are many varieties of mixed and transitional forms between these main groups.

II. With these points fixed, we already have a good basis

from which to consider the second question proposed for discussion, *i.e.*, the possible parasitic origin of cancer; for if the primary cancer, with all its metastases, histologically and histogenetically, is nothing more than a great family of epithelial cells, all of which have a common origin from preformed epithelium, then it is not possible for a parasite to be the chief etiological factor, as in the diseases which are known to be parasitic, such as a pus focus or an infectious granuloma. The pus focus is a purely local manifestation, be it either a primary or metastatic pus focus. Tubercular foci, gumma, leprosy, etc., are purely local developments wherever they occur, whether they are primary or secondary foci; there is never any tissue connection between primary and secondary pus foci, between primary and metastatic tubercular growths.

In order to produce pus, or tuberculosis, etc., it is sufficient for the pus cocci, or tubercle bacilli, to reach suitable media; to bring about a secondary cancer, it is absolutely necessary that cancer cells from the primary or from a similarly created secondary tumor shall reach the particular spot, and there continue their growth. In the case of secondary cancers, we have to do with a successful transplantation of cancer cells; in the case of pus foci, or tuberculosis, there occurs a transplantation of the parasites, which do not themselves form the new focus, but they impel the local tissue, without any co-operation of the tissue of the primary focus, to certain pathological changes. Therefore there is an important difference between these two classes of phenomena; and one cannot conclude, that since in the case of pus foci, tuberculosis, etc., parasites play a rôle, this must also necessarily be the case in the carcinomatous new growths; one can, however, say, that if in cancer, parasites should happen to play a part, then these parasites must be of an entirely different kind than those above-mentioned, because they must bear the closest relationship to the cancer cells which characterize the growth. I do not consider it impossible for an intracellular parasite to play a part here; but it is impossible for it to play an independent part. It cannot possibly in itself be the decisive factor in the new growth; it cannot determine

the variety and the character of the new growth, since the cells themselves, and only they, do this.

I hold that the occurrence of such a parasite is not impossible; but how can we establish their presence?

Experiments to prove the power of transmission of tumors from one individual to another cannot in themselves demonstrate anything at all in this connection, for they only deal with transplantation of tissue to another individual. Just as periosteum transplanted to another animal has the power in its new host to grow and to form cartilage and bone; just as, to choose a still more analogous example, epidermis cells may be transplanted to a wound surface of another individual, and there attain a vigorous growth, so it is in the cases of successful tumor transplantation; in this case we have to do with only the production of a secondary tumor, a metastasis; upon a second individual, parasites need play no part whatever.

If it had been possible to produce tuberculosis only through the medium of tubercular tissue, then it could never have been proven that tuberculosis is caused by the tubercle bacilli. Only through the fact that the same result could be obtained by using pure cultures of the bacilli, entirely independent of the tissue elements as by using tubercular tissue; only through the fact that by means of pure cultures of the bacilli primary tuberculosis can be again reproduced in suitable animals; only by means of this could the parasitic nature of tuberculosis be absolutely established.

It is a matter of no consequence etiologically, in proving the transplantability of cancer, to produce a secondary cancer even upon another individual; but it is of consequence to produce a primary tumor. As long as that is not successfully accomplished, and that by means of an organism in pure culture, so long is also the parasitic nature of cancer not proved.

But now there remains one further question to decide, namely this, whether, according to the present state of our knowledge, we must not accept the parasitic origin of cancer. Long before the parasites of the infectious diseases were discovered, there could be no doubt that such must exist, and even

to-day such diseases are not wanting. (I mention only syphilis, in which we do not know the parasitic factors, but still do not doubt that they must be present.) Is the case of cancer analogous?

What is to be explained in cancer is the limitless and aberrant growth of epithelial cells. I cannot, and will not here go into an explanation of this problem. The case throughout is not such that a satisfactory explanation can be arrived at through the assumption of parasitic activity, rather that we are in a good position to comprehend all the phenomena in the morphology and biology of carcinoma without parasites.

The following are the conclusions which I have arrived at in respect to the parasitic etiology of carcinoma: (1) *No one up to the present time has produced proof that carcinoma is of parasitic origin;* (2) *There is no necessity to assume a parasitic etiology in carcinoma.*